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Molecular Characterization and Antibiotic Resistance Profile of *Staphylococcus haemolyticus* in Pregnant Women with Urinary Tract Infections

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ABSTRACT

Background and Aim: *Staphylococcus haemolyticus* is a prominent pathogen in hospital-related infections, exhibiting high antibiotic resistance. This study aimed to investigate antibiotic sensitivity, biofilm formation, and the presence of virulence-associated genes in *S. haemolyticus* isolated from pregnant women with urinary tract infections.

Materials and Methods: Clinical samples were collected from pregnant women with urinary tract infections between October 2021 and December 2022. *S. haemolyticus* isolates were identified using cultural, biochemical, and molecular methods. Antibiotic susceptibility was determined using the VITEK-2 system. Biofilm formation was assessed, and virulence-associated genes (*hla*, *hlb*, *fnbA*, and *fnbB*) were detected using PCR.

Results: Among 260 clinical samples, 36 *S. haemolyticus* isolates were identified. The isolates exhibited high resistance to Benzylpencillin, Erythromycin, oxacillin, Trimethoprim/sulfamethoxazole, Levofloxacin, and Gentamicin. Resistance was lower to Tigecycline, linezolid, tobramycin, Rifampin, vancomycin, Moxifloxacin, Tetracycline, and Ticoplanin. Biofilm formation was negative in 69.4% and weak in 30.6% of isolates. The *hla* gene was present in all isolates, while *hlb* was detected in 77.7%. Detection rates of *fnbA* and *fnbB* were 88.8% and 38.8%, respectively.

Conclusion: This study highlights the high antibiotic resistance, limited biofilm formation ability, and prevalence of virulence-associated genes in *S. haemolyticus* isolates from pregnant women with urinary tract infections. These findings underscore the clinical significance of this bacterium and the need for infection control measures.

Keywords: *Staphylococcus haemolyticus*, Antibiotic resistance, Biofilm formation, Haemolysins

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1. Introduction

Staphylococcus haemolyticus is a commonly encountered pathogen responsible for staphylococcal infections and is the predominant and clinically significant species among Coagulase-negative staphylococci (CoNS) **(1-4)**. The rapid adaptation and development of antibiotic resistance, including methicillin resistance, and its ability to persist in healthcare settings underscore the significance of multi-resistance in assessing the risk posed by this pathogen **(5-7)**. Methicillin-resistant *S. haemolyticus* isolates have been associated with sepsis and increased patient morbidity and mortality rates, thus emphasizing the clinical impact of antibiotic resistance **(8-10)**. Moreover, *S. haemolyticus* demonstrates remarkable versatility and adaptability within the hospital environment and medical devices, making it a key contributor to nosocomial infections **(11, 12)**.

Staphylococcus haemolyticus is frequently isolated from human urine and wound swab cultures, ranking second only to *Staphylococcus epidermidis* among CoNS species. It plays a pivotal role in healthcare-associated opportunistic infections, particularly those related to implanted medical devices. Among CoNS, *S. haemolyticus* exhibits the highest level of antibiotic resistance, with common heteroresistance to glycopeptides **(13-15)**. Its capacity to develop biofilms and colonize hospital environments further contributes to its persistence and pathogenicity, leading to infections such as endocarditis, urinary tract infections, septicemia, and peritonitis. The genome of *S. haemolyticus* encodes enzymes involved in forming the polygamma-glutamate capsule, which provides defense against cationic antimicrobial peptides **(1, 16, 17)**.

Staphylococcal hemolysins, classified into four toxin types (alpha, beta, gamma, and delta), play a significant role in the virulence of *S. haemolyticus*. The *hla* gene, encoding a pore-forming cytotoxin (PFT), targets various human cell types and acts as a detergent on erythrocytes. Another notable feature of *S. haemolyticus* is its capacity to form biofilms. Bacterial exopolysaccharides generated during biofilm formation may restrict growth and promote the formation of structured biofilms **(18-20)**. Additionally, fibronectin, a glycoprotein found in host tissues, facilitates adhesion between Staphylococcus aureus cells and host cells, playing a crucial role in eukaryotic cell adhesion **(21, 22)**.

This study aimed to investigate antibiotic sensitivity, biofilm formation capabilities, and the presence of virulence-associated genes (*hla*, *hlb*, *fnbA*, and *fnbB*) in *S. haemolyticus* isolates. Our study uniquely focuses on pregnant women with urinary tract infections caused by *S. haemolyticus*. Employing a comprehensive approach, including molecular characterization, antibiotic resistance profiling, and assessment of virulence factors and biofilm formation, we sought to provide accurate insights into the pathogenicity and antimicrobial resistance mechanisms of *S. haemolyticus*. By addressing these research gaps, our study contributes valuable knowledge to the field, enabling the development of tailored prevention and treatment strategies for this population.

2. Materials and Methods

This study was conducted in Al-Rifai General Hospital from October 2021 to December 2022 to isolate *S. haemolyticus* from clinical samples. The study obtained ethical approval from the Iraqi Ministry of Health. A total of 260 urine swab samples were cultured on CLED agar (Cystine Lactose Electrolyte-Deficient agar) obtained from (Oxoid, Ltd., Basingstoke, Hampshire, England). The suspected *S. haemolyticus* isolates were subjected to mannitol fermentation, catalase, and coagulase tests followed by API staph identification. Further confirmation of identification was conducted using the VITEK-2 system. Antibiotic sensitivity testing was also conducted using the VITEK-2 system with relevant cards to confirm the susceptibility patterns of isolated *S. haemolyticus* strains against different antibiotics. Semi-quantitative determination of biofilm formation was carried out following the microtiter plate assay method.

The biofilm production assay was performed using the microtiter plate method. Overnight cultures of *S. haemolyticus* isolates were diluted in tryptic soy broth supplemented with glucose and added to 96-well microtiter plates. After 24 hours of incubation at 37°C, non-adherent cells were removed by washing, and the biofilms were fixed with methanol and stained with crystal violet. OD570 values were measured after solubilizing the stain with acetic acid. Biofilm production was categorized as negative (OD570 ≤ 0.1), weak (0.1 < OD570 ≤ 0.5), or strong (OD570 > 0.5) based on the optical density values.

The DNA was extracted from *S. haemolyticus* isolates using the PrestoTM Mini gDNA Bacteria Kit Quick Protocol (Geneaid), and PCR amplification was performed to detect the presence of virulence-associated genes (*hla*, *hlb*, *fnbA*, and *fnbB*) in the *S. haemolyticus isolates*. The primer sequences used for the amplification of each gene as well as the expected PCR product size are included in Table 1. Moreover, Table 2 provides details of the PCR cycling parameters and conditions used to detect these genes.

Table 1. The primer sequences and expected PCR product size of each gene

The gene	The primer sequences	Expected PCR product size
hla	Forward primer: 5'-ATGAAAAAGCCTGAAAGAA-3' Reverse primer: 5'-TTATTTTACATCCATACTTATG-3'	800 base pairs
hlb	Forward primer: 5'-TCTAATGATTTGACTAAAGT-3' Reverse primer: 5'-TTACTTATTTTATGTTTGGT-3'	900 base pairs
fnbA	Forward primer: 5'-ATGAAAAAGCCTGAAAGAA-3' Reverse primer: 5'-TTATTTTACATCCATACTTATG-3'	1000 base pairs
fnbB	Forward primer: 5'-TCTAATGATTTGACTAAAGT-3' Reverse primer: 5'-TTACTTATTTTATGTTTGGT-3'	1200 base pairs

Table 2. PCR Cycling Parameters and Conditions

PCR steps	Temp.	Time	Repeat
Initial Denaturation	95 °C	5min	1 cycle
Denaturation	95 °C	30sec.	1 cycle
Annealing	55 °C [a, b]	30sec.	38 cycles
Extension	72 °C	1 min.	1 cycle
Final extension	72 °C	5min.	1 cycle

3. Results

In this study, a total of 260 clinical samples were tested, from which 36 *S. haemolyticus* isolates were identified. The antibiotic resistance profile of these isolates was assessed as illustrated in Figure 1, revealing a high level of resistance to multiple antibiotics. The isolates demonstrated complete resistance to Benzylpenicillin (100%) and high resistance rates to Erythromycin (88.8%), Oxacillin (80.55%), Trimethoprim/ sulfamethoxazole (80.55%), Levofloxacin (72.22%), and Gentamicin (55.55%). On the other hand, lower resistance rates were observed for Tigecycline (0%), Linezolid (11.11%), Tobramycin (27.77%), Rifampin (36.11%), Vancomycin (36.11%), Moxifloxacin (41.66%), Tetracycline (44.44%), and Ticoplanin (52.77%). Statistical evaluation of antibiotic resistance demonstrated a significant difference (p=0.0001) between resistant and sensitive isolates for all tested antibiotics, except for Moxifloxacin, where no significant difference ($p > 0.05$) was observed.

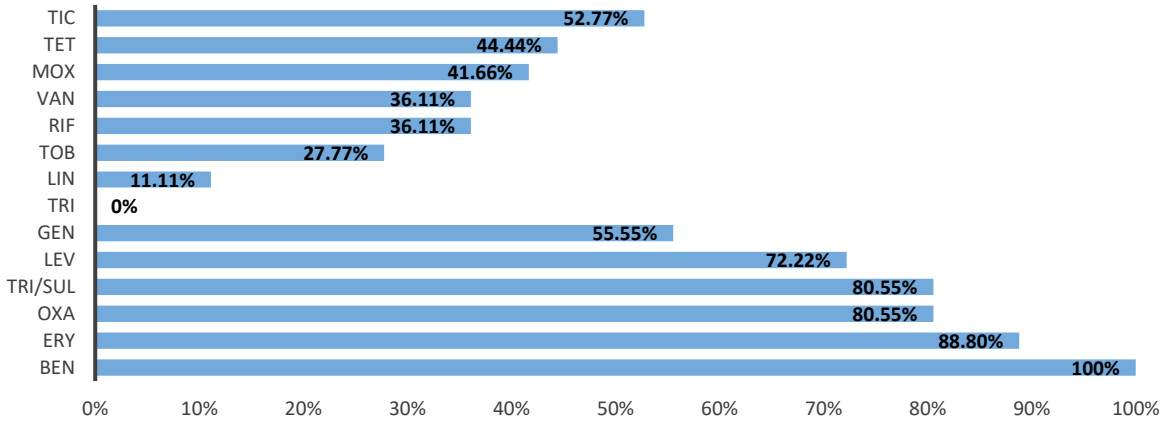

Figure 1. Antibiotic Resistance Profile of *S. haemolyticus* Isolates, where TIC= Ticoplanin, TET= Tetracycline, MOX= Moxifloxacin, VAN= Vancomycin, RIF= Rifampin, TOB= Tobramycin, LIN= Linezolid, TRI= Tigecycline, GEN= Gentamicin, LEV= Levofloxacin, TRI/SUL= Trimethoprim/sulfamethoxazole, OXA= Oxacillin, ERY= Erythromycin, and BEN= Benzylpencillin

Furthermore, this study investigates the biofilm formation capabilities of *S. haemolyticus* and explore the presence of virulence-associated genes. The analysis revealed a PIA-independent biofilm formation in *S. haemolyticus*, distinguishing it from ica-negative isolates. Among the 36 isolates tested, 25 (69.4%)

were found to be negative for biofilm formation, while 11 (30.6%) showed weak biofilm formation. No isolates exhibited strong biofilm formation. Notably, all 36 isolates demonstrated the presence of the α-hemolysin gene (*hla*), while the β-hemolysin gene (*hlb*) was detected in 28 out of 36 isolates, representing 77.7% of the samples, as determined through PCR analysis. Additionally, the prevalence of Fibronectin A (*fnbA*) and B (*fnbB*) genes was observed in 88.8% and 38.8% of the isolates, respectively, as shown in Table 3. To further corroborate these findings, gel electrophoresis was employed, visually confirming the amplified presence of these virulence-associated genes (Figure 2: (a) *fnbB* gene, (b) *fnbA* gene, (c) *hla* gene, and (d) *hlb* gene).

Table 3. Presence and Absence of Genes in the Samples

Gene	No. of samples	No. of positive samples	No of negative sample	Percentage of sample positive
α-Hemolysin	36	36	0	100 %
ß-Hemolysin	36	28	8	77.7 %
Fibronectin-Binding Proteins A	36	32	4	88.8 %
Fibronectin-Binding Proteins B	36	14	22	38.8 %
Chi-Square: χ^2 (P-value)	---	---	---	10.372 ** (0.00982)

** (P≤0.01)-Highly Significant.

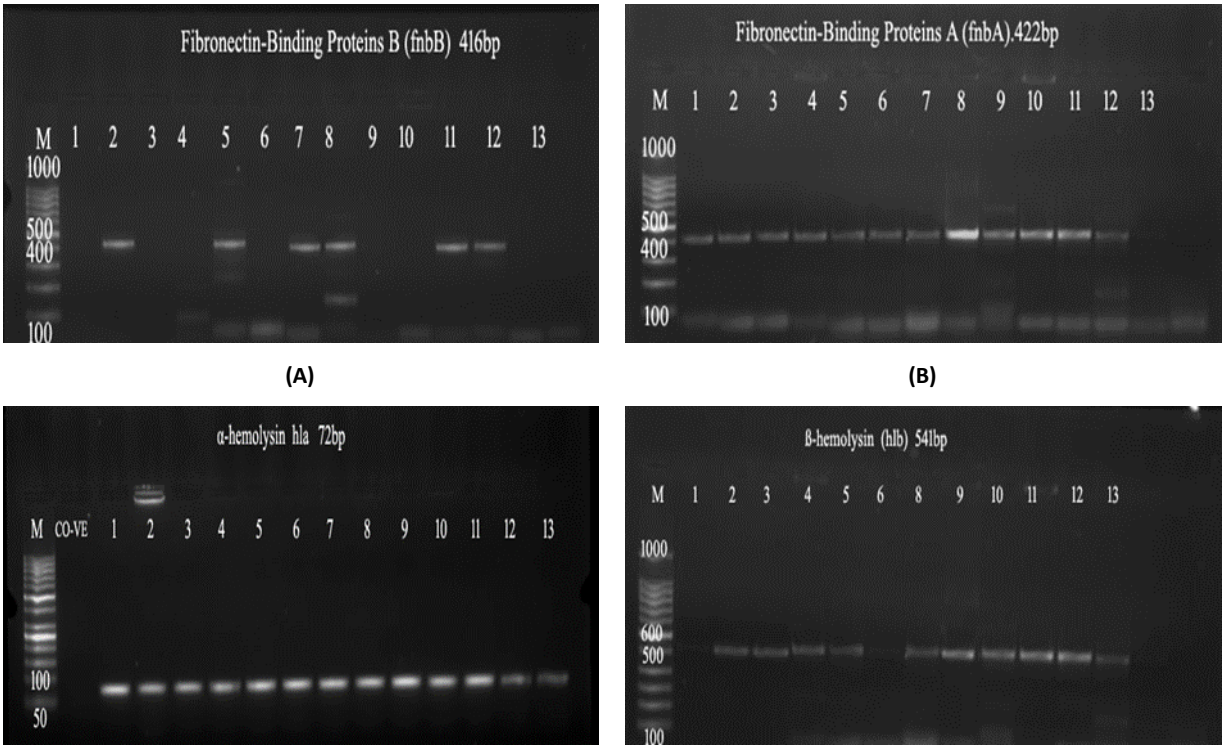

Figure 2. Gel electrophoresis of (a) *fnbB* gene, (b) *fnbA* gene, (c) *hla* gene, and (d) *hlb* gene in *S. haemolyticus*

Moreover, Table 4 presents the types of drug resistance observed in the *S. haemolyticus* isolates. Multiple drug resistance (MDR) was highly prevalent, accounting for 91.7% of the isolates. Three isolates (8.3%) exhibited extensive drug resistance (XDR). No isolates showed pan drug resistance (PDR). To determine these resistance patterns, we assessed the susceptibility of *S. haemolyticus* isolates against a panel of different antibiotics using the VITEK-2 system. The isolates that showed resistance to two or more classes of antibiotics were classified as MDR, while those resistant to nearly all but two or fewer antimicrobial categories were classified as XDR. Isolates that displayed resistance to all agents in all antimicrobial categories were classified as PDR.

Table 4. Types of Drug Resistance in *S. haemolyticus* Isolates

Type of resistance	No. of isolates	Percentage of sample (%)
DR	0	0
MDR	33	91.7
XDR	3	8.3
PDR	0	0
Total	36	100

DR=drug resistance, MDR=Multiple drug resistance, XRD=Extensive Drug Resistance, PDR= Pan drug resistance

4. Discussion

The current study revealed a high level of antibiotic resistance among *S. haemolyticus* isolates, with multiple antibiotics showing high resistance rates. Complete resistance was observed for Benzylpenicillin, followed by high resistance rates for Erythromycin, Oxacillin, Trimethoprim/ sulfamethoxazole, Levofloxacin, and Gentamicin. These findings are consistent with previous studies **(23, 24)** and suggest that *S. haemolyticus* has become increasingly resistant to multiple antibiotics.

Sing et al. reported a lower resistance rate to Erythromycin (17%) in their *S. haemolyticus* isolates **(25)**. On the other hand, Tigecycline, Linezolid, Tobramycin, Rifampin, Vancomycin, Moxifloxacin, Tetracycline, and Ticoplanin showed lower resistance rates in this study compared to previous reports. However, an Iraqi research study reported a Linezolid resistance rate of 4.35% among *S. haemolyticus* isolates **(26)**. The rising resistance to Linezolid raises concerns, as it is frequently used for gram-positive cocci infections **(23)**. Resistance to Linezolid may be caused by mutations in the *cfr* or 23S rRNA gene (24). Whole-genome sequencing revealed the remarkable genomic flexibility and phenotypic acquisition of antibiotic resistance in *S. haemolyticus* **(25)**.

In our study, Tigecycline, a glycylcycline antibiotic, showed complete sensitivity, consistent with previous findings **(27)**. Additionally, combining Tigecycline with Rifampin has been found to have a strong impact on biofilm-forming *S. haemolyticus* **(28)**. This suggests that Tigecycline, alone or in combination with other antibiotics, could be a potential treatment option for *S. haemolyticus* infections. Statistical analysis of antibiotic resistance revealed a significant difference ($p=0.0001$) between resistant and sensitive isolates for all tested antibiotics, except for Moxifloxacin, where no significant difference ($p > 0.05$) was observed. This indicates that the observed resistance patterns are not due to chance.

Biofilm formation in *S. haemolyticus* appears to be Polysaccharide Intercellular Adhesin (PIA)-independent, as biofilm formation has been reported in ica-negative isolates. Similar research conducted by **(29)** has shown that *S. haemolyticus* and other staphylococci isolated from community contexts lacked the *icaAD* and *bap* genes **(30)**. These findings suggest alternative mechanisms may be responsible for biofilm formation in *S. haemolyticus* strains.

The presence of the α-hemolysin gene (*hla*) was detected in all 36 *S. haemolyticus* isolates, while the β-hemolysin gene (*hlb*) was present in 28 out of 36 isolates. This indicates a high prevalence of these hemolysin genes in *S. haemolyticus* strains, which may contribute to their virulence. The presence of Fibronectin A (fnbA) and B (fnbB) genes in *S. haemolyticus* isolates suggests that fibronectin-binding proteins may play a role in bacterial attachment to surfaces and biofilm formation.

The high prevalence of multiple drug resistance (MDR) among *S. haemolyticus* isolates is consistent with previous studies **(29, 31)**. The widespread use of antimicrobial agents, acquisition of mobile genetic elements, genomic rearrangements, and mutations are factors that contribute to the emergence of antibiotic resistance in *S. haemolyticus*. The resistance to Vancomycin and Linezolid is particularly concerning, which highlights the clinical impact of *S. haemolyticus*, especially as methicillin-resistant strains have become common nosocomial pathogens **(32)**. It is imperative to address the challenge of antibiotic resistance in *S. haemolyticus* for effective infection control in healthcare settings **(30)**.

5. Conclusion

In conclusion, this study sheds light on the pathogenicity and antimicrobial resistance of Staphylococcus haemolyticus. The isolates exhibited high resistance rates to various antibiotics, with complete resistance to Benzylpenicillin and concerning

trends in Linezolid resistance. The presence of virulence-associated genes, including *hla* and fibronectin-binding proteins fnbA and fnbB, underscores their potential role in the pathogenicity of S. haemolyticus. Biofilm formation appears to be PIA-independent. The prevalence of multiple drug resistance (MDR) highlights the urgent need for effective infection control in healthcare settings. This research provides valuable data for tailored prevention and treatment strategies, contributing to the understanding and managing *S. haemolyticus* infections.

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Conflict of Interest

The authors declare no conflict of interest.

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