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Detection of the Quaternary Ammonium Compound Antiseptic Resistance Gene (qacA/B, qacC and qacE genes) among *Staphylococcus aureus* Recovered from Wound Infection

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Abstract

Background: Quaternary ammonium compounds (QACs) have represented one of the most visible and effective classes of antiseptics and disinfectant substances that are used in different parts of life including food production, water treatment, and healthcare such as hospitals to prevent infections and intoxications. The increased use of disinfectants containing QACs has raised concerns about the development of QAC resistance.

Objective: To determine the frequency of antiseptic-resistant QACs (qacA/B qacC and qacE gene) among *Staphylococcus aureus* (*S. aureus*), recovered from topical wound infection.

Methods: Two swab samples were collected from 200 patients complaining of burns, traumatic injury, and wounds after surgery, suspected isolates of *S. aureus*, which showed beta hemolysis on blood agar media further tested by inoculated on mannitol salt agar and incubated at 37°C for 24 hours, bacteria that showed the characteristic of the yellow colony were furthermore identified using VITEK-2 System. The efficacy of antiseptics Chlorhexidine (CLX), Benzalkonium (BZK), and Cetrimide was tested against *S. aureus* by well diffusion assay test and minimum inhibitory concentration procedure. The confirmed *S. aureus* isolates have been used for genomic DNA extraction from a fresh overnight culture after that DNA template was used to target (qacA/B, qacC and qacE gene) by using specific Primers sequences.

Results: Of 71 *S. aureus*, a considerable number of isolates 68 (95.8%) were resistant to CLX. Moreover, a substantial number of isolates 67 (94.4%) resistant to Cetrimide. No sensitive rate to BZK was observed in all isolates. qacA/B gene was identified in 48 (67.6%), while qacC gene was detected in 66 (93.0%). Furthermore, qacE gene was detected in 69 (97.2%) of 71 *S. aureus* isolates.

Conclusion: qacA/B, qacC and qacE genes that harbored resistance to QACs antiseptics are widespread among *S. aureus* isolates in wound and burn patients.

Keywords: Quaternary ammonium compound, antiseptic resistance gene, Chlorhexidine (CLX), Benzalkonium (BZK), Cetrimide.

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List of abbreviations: BZK = Benzalkonium, CLSI = Clinical and Laboratory Standards Institute, CLX = Chlorhexidine, MIC = Minimum inhibitory concentration, QACs = Quaternary ammonium compounds

Introduction

The use of disinfectants is widespread in various industries, including healthcare, food production, and water treatment, to prevent infections and intoxications.

Antimicrobial resistance, which is a concern, can be caused by the use of disinfectants. Resistance to disinfectants has been relatively overlooked, despite the significant attention given to antibiotic resistance. This may be due to the lack of a widely accepted definition of disinfectant resistance and the modest increases in susceptibility typically observed [(1)].
Quaternary ammonium compounds (QACs) which belong to a cationic surfactant group of disinfectants it's an important antiseptic and disinfectant in a range of industries and healthcare facilities because they offer several benefits over other regularly used disinfectants. Possessing qualities like low toxicity, high surface activity, and no corrosion [(2)].
QACs tolerance or resistance mechanisms include changes in bacterial cell wall structure, changes in cell membrane function, efflux pumps, and biofilm formation. The development of tolerance or resistance to QACs and antibiotics has been demonstrated by laboratory studies. As well, tolerance to benzalkonium (BZK) was correlated with clinically defined antibiotic resistance [(3)].
The qac genes are a family of multidrug resistance (MDR) genes found in bacteria. These genes encode for efflux pumps that are capable of pumping out a variety of toxic compounds from the bacterial cell, thereby conferring resistance to multiple antibiotic classes. Furthermore, Qac genes code for antiseptic resistance [(4)]. Several qac genes have been reported, including qacA/B genes, qacC/D, qacE/F, qacG, qacH, qacJ, and qacZ. Gram-positive bacteria frequently have qacA/B genes followed by qacC/D genes, whereas Gram-negative bacteria typically have qacE genes [(4)]. These genes have been found in various bacterial species, and they can confer resistance to a range of compounds, including antibiotics, disinfectants, and dyes. The qac genes are named after the first member of the family to be discovered like the qacA gene found in *Staphylococcus aureus* (*S. aureus*) [(5)]. This study strives for the determination frequency of antiseptic-resistant QACs (qacA/B, qacC, and qacE gene) among *S. aureus* isolates recovered from topical wound infection

Methods

The current cross-sectional investigation involved wound and burn swab samples, which were collected from different hospitals in Baghdad, Iraq, during the period from August 2022 to November 2022. It was carried out in a total of 200 patients (male and female) who were clinically suspected to have a bacterial infection of burn, traumatic injury, and wound after surgery. Two swab samples from each participant were collected aseptically, by rotating the sterile cotton swab stick over the selected area as deep as possible for 10 seconds before wound cleaning and dressing one of the swabs was inserted into a sterile transport tube media, while the second one used for direct detection by using the Gram stain procedure [(6)].
The collected swabs were inoculated on blood agar, then incubated at 37°C for 24 hr at the aerobic conditions for cultivation of the isolated bacteria, Suspected isolates of *S. aureus*, which showed beta hemolysis on blood agar media further tested using Gram stain in which, *Staphylococcus species* appeared as Gram-positive clusters or grape-like morphology and then inoculated on mannitol salt agar and incubated at 37°C for 24 hr. Bacteria that showed the characteristic of the yellow colony were furthermore identified using VITEK-2 System according to the manufacturer instructions (bioMérieux company). "The current study was approved by the Institutional Review Board (I.R.B.) in Al-Nahrain University College of Medicine" (in: August - 10th-2022/No.271)

Antiseptic susceptibility

Well diffusion assay test and minimum inhibitory (MIC) concentration.

The efficacy of antiseptics chlorhexidine (CLX), BZK, and Cetrimide was tested against *S. aureus*, the bacteria were cultured in test tubes

containing 2 ml of brain heart infusion broth. The tubes were incubated at 37°C for 24 hr. The inoculum density of selected bacteria was adjusted using 0.5 McFarland standard tubes and then plated onto Muller-Hinton agar in three directions by dipping sterile swabs in suspension. Wells (6 mm diameter) were punched in the plates using a sterile stainless-steel borer. Fifty µl of each antiseptic mentioned above were placed with concentrations ranging from 125 mg/ml to 31.25 mg/ml. Distilled water was used as a negative control; culture plates were incubated at 35°C for 72 hr. When the incubation was complete, the diameter of the inhibition zone around the well was measured and compared with a clinical laboratory institute (CLSI) [7]. In addition to that minimum inhibitory concentration of antiseptics (chlorhexidine (CLX), benzalkonium (BZK), and Cetrimide was determined by a standard agar dilution method according to the CLSI [8].

Molecular assay for detection of qacA/B, qacC, and qacE genes in Staphylococcus aureus isolates

The confirmed *S. aureus* isolates have been used for genomic DNA extraction from a fresh overnight culture by using Geneaid Presto™ Mini gDNA Bacteria Kit (Taiwan) After that DNA templates were used to target (qacA/B, qacC, and qacE gene) by using specific primers sequences which were listed in the table (1).

Table 1. Primer sequences used for detection of quaternary ammonium compounds (QACs) genes

Name of the gene	Seq.	Annealing Temp. (°C)	Size	Reference
qacA/B	F- 5' CTATGGCAATAGGAGATATGGTGT 3' R-5-CCACTACAGATTCTTCAGCTACATG 3'	55	321bp	[9]
qacC	F-5'-GGCTTTTCAAAATTTATACCATCCT-3' R-5'-ATGCGATGTTCCGAAAATGT-3'	56	249 bp	[10]
qacE	F-5´TAGCGAGGGCTTTACTAA GC3´ R-5´CCCATACCTACAAAGCCCCA3´	58	207bp	[11]

Conventional monoplex polymerase chain reaction (PCR) technique was carried out to amplify fragments of qacA/B (321 bp), qacC (249 bp) and qacE (207 bp) genes separately. PCR cycling program parameters used in this reaction for (qacA/B, qacC, and qacE) genes detection and amplification protocol are initiated according to Ergun et al. [9], Khudair and Mahmood [10] and Chen et al. [11].

Statistical analysis

All data were analyzed using statistical package for social sciences (SPSS) version 20. Binomial variables were expressed as numbers and percentages. Due to the descriptive nature of the study, no inferential statistical tests were applied.

Results

Staphylococcus isolates distribution according to type of injury

In this study, out of 159 positive bacterial cultures from patients; as many as 98 (61.6%) of them were recovered from wound injury; of them, 56 (57.1%) were *S. aureus*, in addition to that 61 (38.4%) of the total isolates regained from burn injury; in which, *S. aureus* was 15 (24.5%) (Table 2).

Table 2. Staphylococcus isolates distribution according to type of injury

Type of injury	Number of *S. aureus*
Wound	56
%Within type of Bacteria	57.1%
% of total isolates	35.2%
Burn	15
%Within type of bacteria	24.6%
% of total isolates	9.4%
Total *S. aureus*	71 (44.7%)

Antiseptic resistance of *S. aureus* isolates by well-diffusion method

By the well-diffusion method, *S. aureus* isolates were tested for their susceptibility to CLX, BZK, and Cetrimide. Of 71 *S. aureus* a considerable number of isolates 68 (95.8%) resistance to CLX and only 3 (4.2%) isolates were sensitive. Moreover, a substantial number of isolates 67 (94.4%) resistance to Cetrimide and only 4 (5.6%) isolates were sensitive. While no sensitive rate to BZK was observed in all isolates of *S. aureus* (Table 3).

Table 3. Antiseptic resistance of *S. aureus* isolates by well-diffusion method

Antiseptic agents	*S. aureus*		Total
	Sensitive	Resistant	
Chlorohexidine	3	68	71
% Within type of bacteria	4.2%	95.8%	100 %
Benzalkonium	0	71	71
% Within type of bacteria	0	100%	100%
Cetrimide	4	67	71
% Within type of bacteria	5.6%	94.4%	100%

MIC of *S. aureus* isolates to antiseptic

The MIC of CLX, BZK, and Cetrimide were determined by a broth dilution method for all Staphylococcus aureus isolates The MIC is the concentration of the greater dilution tube where there was no bacterial growth. The MIC results of 71 *S. aureus* isolates were highly resistant to CLX, and Cetrimide (MIC 512 µg/ml to 256 µg/ml) respectively. Almost all bacterial isolates revealed that high level of resistance with MIC 512 µg/ml to BZK.

Molecular detection of qacA/B, qac C, and qacE genes in *S. aureus* isolates

All 71 *S. aureus* isolates were subjected to conventional PCR amplification studies for the detection of CLX, BZK, and Cetrimide resistance genes. The results of the current study showed that the qacA/B gene was identified in 48 (67.6%) of 71 *S. aureus*; this gene was frequently amplified with products size 321 bp (Figure 1); while qacC gene was detected in 66 (93.0%) out of 71 *S. aureus*, which was frequently amplified with products size 249 bp (Figure 2). Furthermore, the qacE gene was detected in 69 (97.2%) of 71 *S. aureus*, this gene was frequently amplified with products size 207 bp (Figure 3).

Figure 1. Gel electrophoresis (1.5% agarose, 7v/cm^2) of the PCR products, lane (1)100bp DNA ladder; (2-13). Positive sample for qacA/B gene (321bp) lane (1,14,15 and 16) Negative samples.

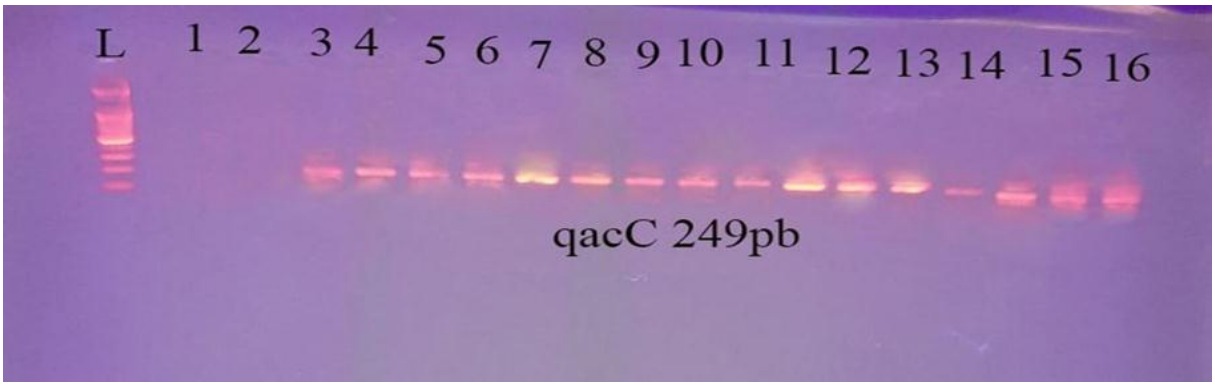

Figure 2. Gel electrophoresis (1.5% agarose, 7v/cm^2) of the PCR products, lane (1) 100 bp DNA ladder; (3-16), positive sample for qacC gene (249 bp) lane (1 and 2) negative samples

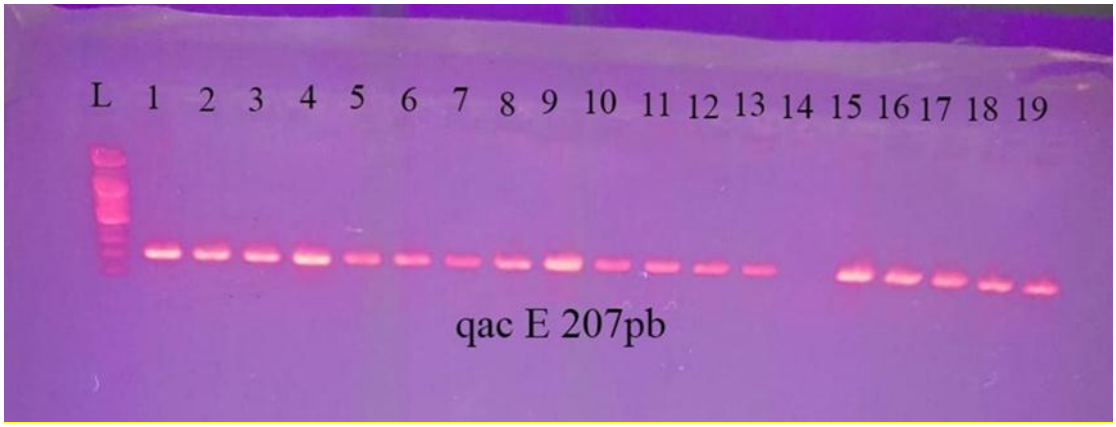

Figure (3). Gel electrophoresis (1.5% agarose, 7v/cm^2) of the PCR products, lane (1)100bp DNA ladder; (1-13 and 15-18). Positive sample for qacE gene (207 bp) lane (14) Negative samples

Discussion

Previous studies mentioned that Biocide used is far less regulated than antibiotic use, leading to concerns regarding the development of biocide tolerance and the possible role these agents play in driving the emergence of MDR pathogens, however the un-responses to antiseptic was highly increased in Gram-positive as well as other Gram-negative species in last years, and the natural resistance mechanism hypothesized to be promoted by mostly driven by the acquisition of genes that provide such resistance [12,13].

As with antibiotics, bacteria also have mechanisms for disinfectant resistance, and one of the problematic situations that can occur is to replace one set of problems (increasing antibiotic resistance) with another (increasing resistance to disinfectants) [14].

Staphylococcus isolates distribution according to type of injury

In this study, out of 159 positive bacterial cultures from patients who presented signs of wound and Burn injury infection; the *S. aureus* comprises 71 isolates (44.6%). *S. aureus* is one of the common pathogens that has been identified as a cause of various nosocomial infections contracted in the community [15]. According to the last investigation, the distribution of *S. aureus* isolated from clinical skin samples varied from country to country and from one hospital to another [16].

Moreover, Wong et al. and Serra et al. reported that; Staphylococcus bacterial species induce more aggressive damage in injury healing due to the ability to express virulence factors and surface proteins which can interfere with wound healing [17,18]. For what concerns type of injuries; the most frequently isolated bacteria from wound and burn injuries was *S. aureus* [19,20].

Antiseptic resistance of *S. aureus* isolates by well-diffusion method

Cetrimide resistance in Staphylococcus aureus was (94.4%), interestingly in this study, no sensitive rate to BZK was observed in all isolates of *S. aureus*. Noteworthy, present results reported that the isolated bacteria of *S. aureus* that showed resistance to antibiotics were also tolerated to antiseptics; in line with these results, there are numerous reports on antimicrobial resistance to antiseptic and antibiotics, at the same time [21,22].

MIC of *S. aureus* isolates to antiseptic

Antiseptics are crucial for stopping the spread of the infection of pathogenic microorganisms when administered properly. Higher MICs of biological agents and the formation of strains resistant to antiseptics and many medications may be the result of improper usage and the

dosage of antiseptics used in hospitals for infection control [23]. Many practical methods have been used to determine MIC, but all of them are based on the same principle. In current research, the MIC values of the study isolates for antiseptic were found to be very high ranging from 512 µg/ml to 256 µg/ml.

In this study, the susceptibility and MIC to CLX, BZK, and Cetrimide were determined because they are widely used as antiseptics and disinfectants in healthcare facilities in our country, this study reported that the high rate of resistance to CLX (95.8%) out of 71 isolates; Cetrimide resistance in *S. aureus* was (94.4%), while; no sensitive rate to BZK were observed in all isolates of Staphylococcus aureus. Concurrent resistance to an antiseptic was noted in many local studies such as Hamad (2019) [24] who noted that, an increase rate of resistance to Dettol (septal), Hepatine, Povidone-iodine to the *S. aureus* isolated from wound and burn infection [25]. Highest proportion of resistance to antiseptics has been reported in other studies globally [26,27].

Decreased susceptibility and acquired resistance to disinfectants have been documented throughout the world primarily against QAC, and phenols components and one of the most common reasons for such dilemma is the misuse of antiseptic in human medicine, food industry, agriculture, and animal production [26,28,29].

Cross-resistance among antibiotics and antiseptics may arise through a variety of shared pathways, involving efflux pump systems, permeability alterations, and biofilm development [30].

Indeed cross- and co-resistance between various types of antiseptic and antibiotic-resistant bacteria have even been reported [31,32]. Russell declares that there is cross-resistance between biocides and antibiotics and the use of biocides selects for antibiotic resistance [33]. Based on this concept, a lot of research has been conducted that confirmed such a hypothesis [27,28,34].

Cross-resistance to antiseptics like QACs and other antibiotics may be explained in part by the presence of antimicrobial resistance genes on mobile genetic elements like plasmids and transposons, microorganisms may acquire the resistance determinants on conjugative plasmids or genetic mobile elements [35].

Plasmid-mediated efflux pumps are crucial defense mechanisms against many antibiotics and antiseptics. Regular use of antibiotics and antiseptics to kill and stop the spread of microorganisms may, in turn, put selective pressure on the retention of resistance genes in microorganisms, including genes or clusters of genes encoding resistance to both antibiotics and disinfectants [36].

Molecular detection of qacA/B, qacC, and qacE genes in *S. aureus* isolates

In this study, a high occurrence rate for QAC genes including qacA/B, qacC, and qacE was detected in *S. aureus*. QacA/B was identified in 48 (67.6%) of 71 *S. aureus*, while qacC was detected in 66 (93.0%), furthermore, QacE was detected in 69 (97.2%). Such results are in line with other broad studies that mentioned an increased detection rate of QAC genes in Gram-positive Bacteria isolated from burns and wound infections [37,38]. The rise in identification rate to QAC genes may be evident in reduced susceptibility to such products of antiseptic. Moreover, expanded and more indiscriminate use of antiseptic in healthcare facilities could ride the emergence of genetic elements that are accountable for reduced susceptibility, with unreliable consequences for human safety. This may be attributed to the extensive use of these types of disinfectants in routine infection control [39].

Although the qac genes are widely spread among clinical and environmental bacteria, it is obvious that their distribution is generally linked with a particular bacterial species. Among Gram-positive bacteria, the qac genes predominate in Staphylococci [40]. Furthermore, in this study, the qacC and qacE genes provide resistance to QAC more than qacA/B such results disagree with studies in the United States [41], European countries [42] and Iran [43]. The mentioned qacA/B genes predominant resistance genes while our results are in part in line with a study by Ignak S et al; who detected the qacA/B genes in (10.3%) [44].

The discrimination in such results may reflect the difference in the specimen source and type of bacteria in each study and may be considered that the antiseptic resistance is a local problem that differed from one hospital to another.

The increasing usage of QAC in healthcare settings has both benefits and potential drawbacks. QAC are commonly used as a disinfectant and hand sanitizer in healthcare facilities due to their antimicrobial properties.

For strains that are resistant to antibiotics, antiseptic application may be employed but the hard scientific fact is that these bacteria can gain resistance to maintain itself in medical facilities

The survival of *Staphylococcus species* in hospital settings may be aided by the link between antibiotic resistance and qac genes. These Staphylococci's endurance in areas with little in the way of antiseptic residues makes them potentially dangerous for infection management.

In conclusion, the current study, shows that the qacA/B, qacC and qacE genes which harbored resistance to QAC antiseptics are widespread among *S. aureus* isolates in wound and burn patients.

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Author contribution

Ahmed: Sampling, data collection and original draft preparation. Dr. Hassan: Data curation and formal analysis investigation and writing. Dr. Mahdi: Methodology, resources.

Conflict of interest

The authors declare that they have no competing interests.

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