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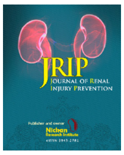

Methicillin-resistant *Staphylococcus aureus* in urinary tract infections; prevalence and antimicrobial resistance

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ABSTRACT

Introduction: The newly-launched strain of the *Staphylococcus aureus*, methicillin-resistant *S. aureus*, is considered the most emerging bacterium in-hospital infections globally.
Objectives: The current research focused on the prevalence and virulence features of methicillin-resistant *S. aureus* (MRSA) bacteria recovered from urinary tract infections (UTIs) cases.
Patients and Methods: A total of 710 urine specimens were taken from hospitalized patients who suffered from UTIs. *S. aureus* was recovered from urine specimens using the microbial culture. *S. aureus* antimicrobial susceptibility was assessed toward oxacillin and cefoxitin antimicrobial disk to determine the MRSA strains. The polymerase chain reaction (PCR) assessed the distribution of antimicrobial resistance encoding genes. *S. aureus* antimicrobial resistance was evaluated by disk diffusion.
Results: Fifty-five out of 710 (7.7%) urine specimens were positive for the MRSA bacteria. The uppermost antibiotic resistance was obtained against penicillin (100%), ceftaroline (100%), gentamicin (87.2%), erythromycin (76.3%), and ciprofloxacin (69.0%). BlaZ (100%) and tetK (85.4%) had the higher frequency amid examined antimicrobial resistance-encoding genes.
Conclusion: The high prevalence of MRSA isolates harboring antimicrobial resistance-encoding genes in the UTIs suggests that diseases caused by them need more expansion healthcare monitoring with essential demand for novel antimicrobials.

Original

Implication for health policy/practice/research/medical education:
The role of the methicillin-resistant *Staphylococcus aureus* (MRSA) has rarely been assessed in urinary tract infections (UTIs). Considering the high pathogenicity of the MRSA bacteria and their high antibiotic resistance attitude toward commonly-used antibiotic agents, it should be determined as an emerging uropathogen. Findings of the present survey revealed that 7.7% of examined urine samples were positive for MRSA. The majority of strains harbored a high prevalence of resistance toward penicillin, ceftaroline, gentamicin, erythromycin and ciprofloxacin antibiotic agents, which was accompanied by the high distribution of antibiotic resistance genes. As a result, more attention should be paid to an antibiotic prescription.

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Introduction

Urinary tract infections (UTIs) are amid the most critical infections kinds globally. UTIs include varieties of disorders, such as urethritis, cystitis, and pyelonephritis. Reports showed that 50% of women had a history of UTIs in their lives. UTIs are thoughtful health issues that concluded 150 million individuals globally yearly (1).

Reports showed that bacteria are the most common cause of UTIs. However, the *Staphylococcus aureus* is not documented as a major pathogen responsible for the occurrence of UTIs, but its prevalence has been increased in recent investigations (2).

Staphylococcus aureus is a significant human pathogen responsible for most cases of nosocomial and hospital-acquired infections. It is responsible for the occurrence of several diseases, including UTIs, respiratory and

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soft tissue infections, endocarditis, osteomyelitis, and endocarditis (3). The bacterium has an emergence of severe antimicrobial resistance. Clinical experiences showed that around 50% of the *S. aureus* isolates harbored complete resistance toward penicillins and cephalosporins groups of antimicrobials (4), which called them methicillin-resistant *S. aureus* (MRSA). MRSA strains caused complicated diseases for a more extended period with a higher economic burden due to hospitalization and treatment (5).

Some genes are involved in the occurrence of antimicrobial resistance amongst the MRSA strains. High distribution of the genes encodes resistance against penicillins (*blaZ*), tetracyclines (*tetK*), macrolides (*msrA* and *ermA*), and fluoroquinolones (*gyrA*) was described in the MRSA isolates of clinical infections (6).

Most UTIs caused by MRSA are healthcare-associated-MRSA (HA-MRSA) infections. Commonly, HA-MRSA's UTI cases are asymptomatic, but symptomatic cases require treatments. However, MRSA strains exhibited whole resistance to all kinds of penicillins and cephalosporins and high resistance toward other antimicrobials types (7).

Objectives

According to the uncertain role of MRSA in UTIs, an existing survey was conducted to evaluate the prevalence and antimicrobial resistance of MRSA bacteria recovered from cases of UTIs.

Materials and Methods

Urine specimens

From January to November 2020, 710 urine specimens were taken from patients referred to the Al-Yarmouk teaching hospitals, Baghdad, Iraq. Patients were hospitalized owing to severe UTIs. Midstream urine was taken through sterile conditions to reduce possible microbial and artifactual contaminations. Urine specimens were taken using sterile glass tubes (10 mL) and immediately transported to the laboratory at 4°C.

Staphylococcus aureus isolation

Sheep blood agar (7%, Merck, Germany) was used for urine specimen inoculation. Media were then incubated for 48 hours at 37 °C. The gram-staining morphologically examined doubtful colonies. Finally, isolates were confirmed using various biochemical tests, including deoxyribonuclease (DNase) test, oxidase, coagulase, and catalase tests, bacitracin (0.04 U) resistance pattern, glucose O/F test, mannitol fermentation test, carbohydrate (mannose, fructose, sucrose, trehalose, xylose, maltose, and lactose) fermentation tests, nitrate reduction, urease activity, and Voges–Proskauer test.

Identification of MRSA isolates

MRSA identification was carried out using oxacillin (1 µg) and cefoxitin (30 µg) susceptibility testing, rendering the Clinical and Laboratory Standards Institute (CLSI) (8).

Antimicrobial resistance testing

Procedures introduced by the CLSI (9) were applied for this goal. Mueller–Hinton agar (Merck, Germany) was used for MRSA's culture. Diverse antimicrobial disks, such as ceftaroline (30 µg/disk), ciprofloxacin (5 µg/disk), gentamicin (10 µg/disk), azithromycin (15 µg/disk), clindamycin (2 µg/disk), trimethoprim-sulfamethoxazole (25 µg/disk), penicillin (10 µg/disk), erythromycin (15 µg/disk), and rifampin (5 µg/disk) were placed on media. Microbial media with placed disks were incubated (24 h at 35°C). Accordingly, guidelines of the CLSI were applied for susceptibility analysis (9).

DNA extraction and quality assessment

Tryptic Soy Broth (TSB) (Merck, Germany) was used for MRSA growth before DNA extraction. DNA extraction kit (Thermo Fisher Scientific, Germany) was applied. The NanoDrop (NanoDrop, Thermo Scientific, USA) device was applied for the quantitative assessment of extracted DNA. Agarose gel electrophoresis (2%) was applied to the qualitative assessment of extracted DNA.

Detection of antimicrobial resistance-encoding genes

Table 1 displays the polymerase chain reaction (PCR) circumstances applied for this goal (10,11). Eppendorf Mastercycler (Hamburg, Germany) device was applied for the amplification. Positive (positive DNA samples of each gene) and negative [PCR-grade water (Thermo Fisher Scientific, Germany)] controls were applied to monitor the findings of the PCR.

Data analysis

Data collected from the experiment were numerically evaluated by the SPSS/22.0. Qualitative data taken from the tests were examined using the chi-square and Fisher's exact and 2-tailed tests. *P* value less than 0.05 was determined as a significance level.

Results

Study population

Table 2 shows the population comprised in the present survey. The mean age of the studied individuals was 53.5 years. The ratio of male to female amongst the studied population was 280/430. The distribution of smoking and alcohol amongst studied patients was 44.9% and 35.2%, respectively. Among all examined clinical findings, dysuria (34.9%) was the most predominant.

Distribution of MRSA and antimicrobial resistance properties

Table 3 represents the prevalence and antimicrobial resistance of MRSA bacteria recovered from urine specimens. Findings showed that 55 out of 710 (7.7%) urine specimens were positive for the MRSA. MRSA

Table 1. Polymerase chain reaction (PCR) procedures used to detect antimicrobial resistance-encoding genes (10, 11)

Genes	Primers (5'-3')	PCR product (bp)	Thermal cycles	Volume (50 µL)
ermA	F: AAG-CGG-TAA-ACC-CCT-CTG-A R: TTC-GCA-AAT-CCC-TTC-TCA-AC	190	**1 cycle** 5 min: 94˚C **25 cycles** 60 s: 94°C, 70 s: 55°C, 60 s: 72°C **1 cycle** 10 min: 72°C	PCR buffer 10X: 5 µL Mgcl2: 2 mM dNTP: 200 µM Primer F: 0.5 µM Primer R: 0.5 µM Taq DNA polymerase: 1.5 U DNA: 5 µL
tetK	F: GTA-GCG-ACA-ATA-GGT-AAT-AGT R: GTA-GTG-ACA-ATA-AAC-CTC-CTA	360		
gyrA	F: AGT-ACA-TCG-TCG-TAT-ACT-ATA-TGG R: ATC-ACG-TAA-CAG-TTC-AAG-TGT-G	280	**1 cycle** 6 min: 94˚C **34 cycles** 50 s: 95˚C, 70 s: 55°C, 60 s: 72°C **1 cycle** 8 min: 72°C	
msrA	F: GGC-ACA-ATA-AGA-GTG-TTT-AAA-GG R: AAG-TTA-TAT-CAT-GAA-TAG-ATT-GTC-CTG-TT	940	**1 cycle** 6 min: 95˚C **34 cycles** 60 s: 95˚C, 70 s: 50°C, 70 s: 72°C **1 cycle** 8 min: 72°C	
blaZ	F: TGA-ACC-GTA-TGT-TAG-TGC R: GTC-GTG-TTA-GCG-TTG-ATA	681	**1 cycle** 6 min: 94˚C **30 cycles** 60 s: 95˚C, 60 s: 59°C· 60 s: 72°C **1 cycle** 10 min: 72°C	

isolates displayed the supreme resistance rate toward penicillin (100%) and ceftaroline (100%). The resistance rate against gentamicin, erythromycin, and ciprofloxacin was 87.2%, 76.3%, and 69.0%, respectively. Table 4 shows the antimicrobial resistance-encoding genes distribution amongst the MRSA isolates. *BlaZ* (100%) and *tetK* (85.4%) had the higher frequencies amongst examined antimicrobial resistance-encoding genes.

Discussion

MRSA strains are measured as one of the most critical reasons for healthcare-associated and community-associated (CA) infections. Both CA-MRSA and HA-MRSA have the emergence of antimicrobial resistance. Reports showed that MRSA strains recovered from clinical infections displayed a considerable prevalence of resistance toward various antimicrobials classes, including cephalosporins, penicillins, quinolones, macrolides, tetracyclines, aminoglycosides, phenols, and lincosamides (12). Thus, it is essential to assess its prevalence and molecular epidemiology amongst diverse kinds of hospital infections.

Table 2. The study population of the present survey

Demographic characters	Individuals (n= 710)
Mean age (SD)	53.5 (13.4)
Gender (M/F)	280/430
Mean weight (SD)	65.1 (13.1)
Mean BMI (SD)	25.4 (4.2)
Smoking (%)	44.9
Alcohol (%)	35.2
Clinical findings	
Fever (%)	24.9
Nausea (%)	11.2
Hematuria (%)	26.0
Dysuria (%)	34.9

The present study showed that 7.7% of the urine specimens of hospitalized patients who suffered from UTIs were positive for the MRSA strains. MRSA isolates displayed a boost resistance rate toward erythromycin, ceftaroline, penicillin, gentamicin, and ciprofloxacin antimicrobial agents. Additionally, MRSA isolates harbored a boost distribution of blaZ and tetK antimicrobial resistance-encoding genes. It seems that the antimicrobial-resistant MRSA isolates may be an emerging cause of UTIs in Iraq.

Similarly, Lunacek et al (7) labelled that the MRSA prevalence amongst urine specimens in Austria was 4.06%. They disclosed that MRSA isolates were resistant toward cephalosporin, aminopenicillin, penicillin G, carbapenem, and β-lactamase antimicrobial agents. They also presented that catheter utilization is the most critical risk factor for MRSA occurrence in UTIs. An Irish survey (13) described that the prevalence of MRSA strains was 27.9%. Besides, MRSA isolates of the urine specimens displayed the

Table 3. MRSA prevalence and antimicrobial resistance amid the studied population

Specimens (N. taken)	N. positive specimens for the MRSA (%)	N. MRSA isolates harbored resistance against each antimicrobial disk								
		P10	Cef	Gen	Az	Ert	Cip	Cln	Tri-sul	Rif
Urine (710)	55 (7.7)	55 (100)	55 (100)	48 (87.2)	26 (47.2)	42 (76.3)	38 (69.0)	34 (61.8)	32 (58.1)	20 (36.6)

P10: penicillin (10 µg/disk), cef: ceftaroline (30 µg/disk), gen: gentamicin (10 µg/disk), az: azithromycin (15 µg/disk), ert: erythromycin (15 µg/disk), cip: ciprofloxacin (5 µg/disk), cln: clindamycin (2 µg/disk), tri-sul: trimethoprim-sulfamethoxazole (25 µg/disk), rif: rifampin (5 µg/disk).

Table 4. Antimicrobial resistance-encoding genes distribution amid the MRSA isolates

Specimens (N. MRSA)	N. MRSA harbored each antimicrobial resistance-encoding gene			
	tetK	***gyrA***	***msrA***	***blaZ***
Urine (55)	47 (85.4)	35 (63.3)	25 (45.4)	55 (100)

tetK: tetracycline-encoding gene, *gyrA*: quinolones encoding gene, *msrA*: Macrolides specific resistance gene, *blaZ*: penicillin encoding resistance gene.

uppermost resistance rate toward flucloxacillin (100%), co-amoxiclav (100%), and ciprofloxacin (98%).

Urinary MRSA is a rarely assessed phenomenon. In a multicenter survey conducted in Britain, *S. aureus* reported only 0.5% of urinary isolates (14). A French survey (15) reported that only 1.3% of isolates from the UTIs were positive for the S. aureus. Pacio et al (16), stated that 13% of MRSA-colonized patients at any site developed symptomatic UTIs.

Unauthorized prescription of antimicrobials and self-treatment with antimicrobials, and indiscriminate use of disinfectants are likely explanations for the boost prevalence of antimicrobial resistance in the present survey. Boost resistance rate of MRSA recovered from human clinical infections toward penicillin, ceftaroline, gentamicin, erythromycin, and ciprofloxacin was also reported from Portugal (17), and United States (18). Onanuga et al (1), discovered that the MRSA isolates of UTIs in Nigeria harbored severe resistance toward ampicillin (100%), tetracycline (97.8%), chloramphenicol (80.4%), cotrimoxazole (73.9%), gentamicin (73.9%), cefuroxime (54.3%), and ciprofloxacin (32.6%) antimicrobial agents. Sina et al (19) designated that the UTIs S. aureus isolates from Benin displayed a high prevalence of resistance toward penicillin (100%), amoxicillin (83.3%), gentamicin (54.1%), erythromycin (50.0%), ciprofloxacin (54.1%), and tetracycline (83.33%), which was similar to our findings. A polish survey (20) showed that MRSA isolates of hospital infections revealed a high prevalence of resistance against ciprofloxacin (83%), clindamycin (72.3%), levofloxacin (83.9%), and erythromycin (77.7%) antimicrobial agents.

Our findings also showed the high distribution of penicillin (*blaZ*)- and tetracycline (*tetK*)-encoding genes amongst the MRSA isolates. Boost distribution of *blaZ*, *tetK*, *gyrA*, ermA, and msrA antimicrobial resistance-encoding genes, amongst other types of infections, has been reported from Malaysia (21), Uganda (22), and Turkey (23). There were several mechanisms of antimicrobial resistance (24). The antimicrobial resistance-encoding genes presence is one of them (25). Thus, it is not surprising that the distribution of antimicrobial resistance-encoding genes was much lower than the antimicrobial resistance pattern of the MRSA isolates toward one group of antimicrobials. However, it is essential to assess the status of antimicrobial resistance-encoding genes amongst MRSA isolates of UTIs.

The present survey was limited to the low groups of examined patients and the absence of assessing the distribution and antimicrobial resistance of MRSA amongst patients with different clinical signs of UTIs.

Conclusion

In conclusion, MRSA strains are considered an opportunist cause of UTIs in Iraq hospitals. According to findings, penicillin, ceftaroline, gentamicin, erythromycin, and ciprofloxacin prescription can not effectively be controlled and treat the MRSA's UTIs in Iraq. However, further surveys should perform to assess other epidemiological features of MRSA in UTIs.

Limitations of the study

The present study was limited to the lack of microbial assessment of urine samples of healthy volunteers as a control group, low numbers of isolated bacteria, and finally, the absence of the disk diffusion analysis of other antibiotic agents.

Authors' contribution

RAK, NA, BWH and MFN were the principal investigators of the study. RAK and BWH carried out the samples collection, bacterial isolation and disk diffusion. NA carried out the MRSA identification and DNA extraction. MFN designed and supported the study and carried out the PCR genetic alignment. FE participated in statistical analysis. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the manuscript's content and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The present examination was performed on the urine specimens of volunteer patients hospitalized in the hospital due to UTIs. Written informed consent was taken from all participants before any intervention. Personal information of the individuals of the study is kept secret. Additionally, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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