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The Occurrence of Type I, II, and III Integrons in Multi-drug Resistance and Methicillin-Resistant *Staphylococcus aureus* Isolates in Iran

Mehrdad Mohammadi[1] · Nikou Bahrami[2] · Mona Khajavian[3] · Jamshid Faghri[4]

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Abstract

Integrons are mobilizable platforms-DNA elements with impacts on moving antibiotic resistance genes among bacteria and capable of spreading multi-drug resistance (MDR) in pathogens. Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are the main cause of community-acquired and nosocomial infections with high mortality and morbidity rates worldwide. This work is mainly aimed at calculating the frequency of Type I, II, and III integrons within multi-drug resistance and Methicillin-resistant *S. aureus* Isolates in Iran. In this cross-sectional study, 230 clinical isolates of *S. aureus* were gathered from patients of educational hospitals in the provinces of Iran. These isolates were verified utilizing particular biochemical examinations and then assessed for antibiotic susceptibility through disk diffusion technique and standard procedures were done. Genomic and plasmid DNA of all isolates were extracted using Extraction Kit and PCR assay was used for the detection of Type I, II and III integrons genes. Out of the 230 *S. aureus* isolates, 136 (59.1%) isolates were MRSA and 141 (61.3%) isolates exhibited the MDR pattern. PCR and sequencing showed that 57 (24.8%) of tested isolates carry Type I integron. Among the isolates investigated, MRSA and MDR isolates showed frequencies of 56.1% and 57.9%, respectively. Type II and III integrons were found in none of 230 isolates. The IntI I gene was present in approximately one-quarter of this study isolates. The great prevalence rate of MDR and MRSA isolates and concurrently the existence of Type I integron among those isolates have been considered an important concern in medical society.

Introduction

Staphylococcus aureus is a non-motile, Gram-positive, facultatively anaerobic, and omnipresent coccus existing in mainly the skin and mucosal membranes of humans [1]. *S. aureus* is in charge of an extensive range of infections, comprising folliculitis, acne, abscess, and wound infections, and life-threatening infections such as sepsis, osteomyelitis, toxic shock syndrome (TSS), food poisoning, bacteremia, and endocarditis [1]. *S. aureus* infections, mostly in pyogenic and acute types, as well as being able to spread to other body tissues *Staphylococcus aureus* is identified as being one of the world's leading sources of hospital-acquired infections [1, 2]. In this case, antibiotic resistance of *S. aureus* is nonetheless a principal concern in the remedy of infectious illnesses owing to the misapplication of traditional antibiotics [1–3].

Methicillin, a β-lactamase-resistant antimicrobial agent, used to be represented in 1959 and the primary reported case of methicillin-resistant *S. aureus* (MRSA) from London in 1961 [3]. It was proposed that the mecA gene is the major cause of resistance to methicillin. mecA encrypts a mutated

✉ Mehrdad Mohammadi
mohammadi-m@kaums.ac.ir

Nikou Bahrami
nikou.bahrami@yahoo.com

Mona Khajavian
moonakhajavian@gmail.com

Jamshid Faghri
jamshid.faghri.bac@gmail.com

[1] Department of Medical Microbiology and Immunology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran

[2] Department of Biology, Faculty of Science, Shahid Chamran University of Ahvaz, Ahvaz, Iran

[3] Department of Microbiology, Yasooj Branch, Islamic Azad University, Yasooj, Iran

[4] Department of Microbiology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

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penicillin-binding protein (i.e., PBP2a) with a low attraction for β-lactam antibiotics [4, 5]. The multi-drug resistance phenomenon, seen principally in MRSA strains, is the main agent of treatment loss and enlarge in treatment costs in healthcare systems [6]. Notably, MRSA infections are correlated to an overhead mortality rate in comparison with methicillin-susceptible *S. aureus* infections [7, 8].

MRSA was formerly supposed as a nosocomial pathogen, however, over the previous 20 years, reports propound an extending drift for community-associated MRSA (CA-MRSA). These clones probably substitute the present healthcare-related MRSA (HA-MRSA) clones in the future. Recent reports have exposed an increment in the global incidence of MRSA [3, 5, 6].

The *S. aureus* turns to MRSA strains by gaining the mecA gene [4]. This acquisition has done by the mobile genetic elements (MGEs) that can move around within a genome, or that can be transferred from one species or replicon to another [6]. The MGEs for instance integrons, transposons, and plasmids are also liable for acquiring and additionally the extent of antibiotic resistance genes [9, 10]. The integrons' function has been conceived inasmuch movable genetic apparatus in the horizontal transferring of the antimicrobial resistance genes in bacteria [11, 12]. Likewise, the integron horizontal transfer is determined as the most potent procedure of extending antimicrobial resistance genes and making multidrug-resistant (MDRs) cases [9]. Besides, diverse types of integrons were determined in terms of the contrariety in their integrase gene elements [9]. The Type I integrons possess the topmost periodicity within Gram-negative bacteria and Gram-positive bacteria separated from medical samples [9, 13]. The Type II integrons possess a lower incidence rate than Type I integrons revealed further in Gram-negative bacteria. Type III integrons emerge to be much less common (ranged from 0 to 10%.) and so are less enthralled in the spread of multidrug resistance [9, 13].

In structurally, the integrons have composed of three DNA sections such as a 5′ conserved section (5′ CS) encoding a recombinase (integrase) [13]. This section admits for site-particular incorporation of drug resistance gene clusters between two greatly retained near head nucleotide sequences 5′ CS and 3′ CS, an inside mutable region with one or further resistance gene cassettes with various sequences and lengths, and a 3′ conserved segment (3′ CS) [9, 10, 13]. The 3′ CS contains a quaternary ammonium compound resistance gene, an unknown function. Moreover, the integrons transfer resistance gene elements in the genetic cassette by consolidation within chromosomes, transposons, and plasmids. The integrons deliver further exuberant antibiotic resistance genes and these genes have a contribution in producing resistance against various antibiotics, such as aminoglycosides, macrolides, β-lactams, chloramphenicol, and sulfonamides [9, 13, 14].

We did not find a recent complete investigation in Iran that indicates all of the integrons in *S.aureus*. For this reason, regarding the frequency of Type I, II, and III integrons in *S. aureus* isolates, we conducted our analysis in four provinces that include Isfahan, Qom, Kashan, and Tehran. Therefore, this work was mainly aimed to calculate the frequency of Type I, II, and III integrons in methicillin-resistant *S. aureus* (MRSA) and multi-drug resistance *S. aureus* (MDR) isolates from clinical samples in the center, Iran.

Materials and Methods

This cross-sectional report was done on 230 strain of *S. aureus* isolated from various samples of patients such as urine, wound, blood, catheter, trachea, abscess, and synovial fluid. These samples were collected at four provinces that including Isfahan (Al-Zahra hospital), Kashan (Shahid-Beheshti), Qom (Shahid Beheshti), and Tehran (Masih-Daneshvari) from January 2018 to September 2019.

All procedures performed in this study were following the ethical standards of the Kashan university of medical sciences, and the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from the patient involved in the study.

The isolates were recognized utilizing standard biochemical examinations such as Gram staining, oxidase disk test (Himedia Co., India), catalase, DNAase (Himedia Co., India), coagulase tube test, mannitol fermentation (MSA, (Himedia Co., India), and Novobiocin susceptibility test (Himedia Co., India). After the ultimate identifying, the isolates of *S. aureus* were analyzed to femA, a cytoplasmic protein essential for expressing the methicillin resistance in *Staphylococcus aureus* included in biosynthesizing the staphylococcal cell [15, 16], the PCR test was done for all isolates.

The antibiotic susceptibility test was done in terms of the Kirby-Bauer disk diffusion technique at turbidity of 0.5 McFarland standards on Mueller–Hinton agar (Himedia Co., India) plates regarding the Clinical and Laboratory Standards Institute guidelines (CLSI 2018 edition) [17].

In our work, 16 antibiotic disks (MAST, UK) were used such as piperacillin/Tazobactam (110 µg), Imipenem (10 µg), Cefuroxime (30 µg), Moxifloxacin (5 µg), Levofloxacin (5 µg), amikacin (30 µg), gentamicin (10 µg), rifampicin (5 µg), tobramycin (10 µg), linezolid (30 µg), penicillin (5 µg), clindamycin (2 µg), vancomycin (30 µg), levofloxacin (5 µg), ciprofloxacin (5 µg), and co-trimoxazole (25 µg) to detect MRSA and MSSA strains. The bacterium suspension was extended on Mueller–Hinton agar medium (Himedia Co., India) after incubating at 37 °C and then compared with a 0.5 McFarland standard. Then, the antibiotic disks were positioned on the medium. The diameters of growth

inhibition area were measured after incubating for 24 h in an incubator and compared with CLSI tables. To control the disk's quality, and *S. aureus* standard strain (ATCC 25923) was utilized for antibiogram test. The positive samples template DNA was made utilizing a Gene MATRIX Quick Blood DNA Purification Kit (EURx Ltd., Gdansk, Poland) based on the instructions of the manufacturer.

The PCR was similarly conducted to determine the genes for femA gene detection and genes of Type I, II, and III integrons via their definite primers (SinaClon Co., Iran) (Table 1). The products have done with an ultimate volume of 25 µL with 12.5 µL of Master Mix (SinaClon Co., Iran), 2 µL of bacterial DNA, 1 µL of each primer, and sterile distilled water to 25 µL. The PCR thermal cycles for integron and femA genes contained primary denaturation for 5 min at 94 °C, after 35 main cycles and an ultimate extension at 72 °C for integron and femA genes for 7 and 2 min, respectively (Table 1) [15, 16]. In the end, the PCR products were examined using the 2% agarose gel electrophoresis and stained with SYBR Safe DNA and visualized and pictured through a transilluminator (UVITEC Alliance 4.7, Bio-Active., Ltd., Bangkok, Thailand). We used femA-negative control and femA-positive control (S. aureus ATCC 33591) (*S.epidermidis* ATCC 2228).

Results

In this report, out of the 230 *S. aureus* isolates, 136 (59.1%) isolates were MRSA and 141 (61.3%) isolates exhibited the MDR pattern. In this report, out of 230 isolates of *S. aureus*, 141 (61.3%) were obtained in men and 89 (38.7%) in women, with a total mean age of, was 44.8 years. The major ward of the hospital that we obtained our samples was an internal ward with 110 samples (47.6%). The greatest isolates frequency was obtained in blood specimens ($n = 32$, 22.7%), urine specimens ($n = 7$, 5%), respiratory tract infusions ($n = 21$, 36.2%), skin and soft tissue samples ($n = 21$, 14.9%), cutaneous ulceration samples ($n = 20$, 14.2%), and catheter samples ($n = 11$, 7.1%). PCR and sequencing showed that 57 (24.8%) of tested isolates carried Type I integron (Fig. 1). Among the isolates investigated, MRSA and MDR isolates showed frequencies of 56.1% and 57.9%, respectively. Among the isolates, MDR and Non-MDR isolates represented integron I frequencies of 23.4% and 26.9%, respectively. The antibiotic susceptibility panel for integron positive isolate is shown in Tables 2 and 3.

Discussion

Staphylococcus aureus is an adaptable and successful human pathogen [4]. The increasing incidence of MRSA and *S. aureus* results in the incremented occurrences of community-acquired and hospital-acquired infections all over the world creating a key public health concern [4, 5]. The horizontal carrying of resistance genes through integrons [10]. This action is a key route of antibiotic resistance [10]. The integrons are mobile genetic elements that pass gene cassettes capable of dispersing MDR isolates and then limit options for treatment for controlling infectious diseases [9]. The presence of these components, in particular Type

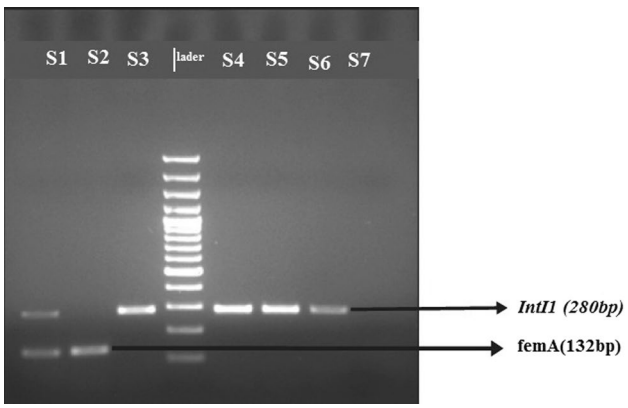

Fig. 1 Electropherogram of PCR amplification products of the class I integron in lanes of 1, 3, 4, 5 and 6 (280 bp). The middle line is DNA marker; and femA gene PCR amplification (120 bp). PCR bands show that the amplification products of class I integron was 280 bp

Table 1 Primer sequences of target genes and lengths of aimed products

Genes	Primers(5′–3′)	Size of amplified product (bp)	References
femA	F-AAAAAAGCACATAACAAGCG	132	[16]
	R-GATAAAGAAGAAACCAGCAG		
IntI I	F-CCTCCCGCACGATGATC	280	[18]
	R-TCCACGCATCGTCAGGC		
IntI II	F-GTAGCAAACGAGTGACGAAATG	788	[19]
	R-CACGGATATGCGACAAAAAGGT		
IntI III	F-GCCTCCGGCAGCGACTTTCAG	433	[20]
	R-GATGCTGCCCAGGGCGCTCG		

Table 2 Results of antibiotic resistance of integron positive isolates vs integron negative isolates of *S. aureus* isolates

Antibiotic	Antibiotic Susceptibility			Integron-positive isolates			Integron-negative isolates			P value
	R (%)	*I* (%)	*S* (%)	*R* (%)	*I* (%)	*S* (%)	*R* (%)	*I* (%)	*S* (%)	
Gentamycin	47	1.3	51.7	10.5	0.4	13.9	36.5	0.9	37.8	0.52
Amikacin	46.1	6.5	47.4	10.9	1.7	12.2	35.2	4.8	35.2	0.88
Tobramycin	47	3.9	49.1	10.5	1.3	13	36.5	2.6	36.1	0.56
Rifampicin	36.5	1.3	62.2	10.4	0.4	13.9	26.1	0.9	48.3	0.41
Penicillin	97.8	0	2.2	24.3	0	0.4	73.5	0	1.7	0.80
Oxacillin	39.6	3	57.4	10.4	0.9	13.5	29.1	2.2	43.9	0.77
Ciprofloxacin	50	6.5	43.5	13.5	1.3	10	36.5	5.2	33.5	0.78
Levofloxacin	43.5	3.5	53	12.2	0	12.6	31.3	3.5	40.4	0.22
Moxifloxacin	42.2	4.3	53.5	11.3	1.3	12.2	30.9	3	41.3	0.71
Co-Trimoxazol	17	0.4	82.6	3.1	0.4	21.3	13.9	0	61.3	0.15
Teicoplanin	4.4	17	78.7	0.9	4.3	19.6	3.5	12.6	59.1	0.93
Clindamycin	37.4	3.9	58.7	10	0.9	13.9	27.4	3	44.8	0.88
Erythromycin	45.2	10.9	43.9	12.2	1.3	11.3	33	9.6	32.6	0.31
Linezolid	2.6	0	97.4	0.9	0	23.9	1.7	0	73.5	0.63
Chloramphenicol	3.5	9.6	87	0	21.7	3	3.5	6.5	65.2	0.21
Tetracycline	58.3	3	38.7	14.8	0.9	9.1	43.5	2.2	29.6	0.88

Table 3 Results of antibiotic resistance of integron positive isolates VS integron negative isolates of *S. aureus* Isolates

Frequency rate	Integron class I			Frequency rate	
Isolates $N = 230$	Positive	Negative	Isolates $N = 230$	Positive	Negative
MDR $N = 141$	33 (23.4%)	108 (76.6%)	MRSA N = 136	32 (23.5%)	104 (76.5%)
NON-MDR $N = 89$	24 (26.9%)	65 (73.1%)	MSSA $N = 94$	20 (26.6%)	69 (73.4%)

I integrons, is one of the causes of the emergence of MDR isolates [11, 13].

Integrons were defined in almost 9% of the bacterial genomes, with Type I integron construction as the most global and most frequently reported one [9, 18]. Numerous reports indicated that this type of integron can capture gene cassettes and encrypt resistance against quaternary sulfonamide and ammonium salts [14]. As the organization of Type I integron, Type II integron is usually related to the Tn7 transposon group. In this study, it was found that the frequency of Type I and II integrons is 47.7% and 17.4%, respectively. Compare with Type II integron, Type III integron includes the same structure, the incidence and recognition rate of Type III integron are in the range of 0 to 10% [9, 11, 13, 14, 19].

In a recent work, performed by Ghasemian et al., in 2015, in 219 strains of *Staphylococcus aureus*, out of 64 methicillin-resistant isolates, 56% had MDR pattern [20]. In another study recently conducted by Diba et al., partners carried out in Ardabil showed that the frequency of 46.3% isolates was MRSA, which were isolated from two teaching hospitals in Ardabil [8]. Also in another study in Iran conducted by Javadi et al. 46.2% of *Staphylococcus aureus* isolates have multiple drug resistance patterns [21]. In the current report in 2019 by Mohammadi et al. in Isfahan that reported a 30% prevalence of MRSA in 150 various clinical specimens [22]. Our findings showed a greater prevalence of MRSA and MDR in comparison with the previous four studies. But according to a study by Rezazadeh et al. (2013) in Arak, 81 (81%) of 111, *Staphylococcus aureus* isolates were able to tolerate methicillin resistance by both phenotypic and genotypic methods [23]. Therefore, our current study has a lower prevalence rate than the previous report.

The results of this study showed that 57 (24.8%) of 231 isolates of *S.aureus* carried the IntI I gene and the frequency of this gene among strains was 23.5% for MRSA and 23.4% for MDR among isolates. Despite extensive studies among gram-negative bacteria, fewer reports exist regarding gram-positive bacteria. However, in the last 2 to 3 years, the existence of integron types has attracted much attention in *S.aureus*.

In Iran, Javadi et al., during a study in Tehran in 118 isolates of *Staphylococcus aureus*, revealed that 31 isolates were positive for the existence of the IntI I gene [21]. In the study of Veise et al. from Iran, among the 200 *Staphylococci* spp., 81 (40.5%) isolates were Type I integron carriers [19]. Our report was same with these two reports that indicated Integron Type I only typed in clinical specimens. But in district report in Iran, in a report by Mostafa et al. in Tehran, Iran in 2015, they reported amongst 139 *S. aureus* isolates,

112 (80.5%) and 109 (78.4%) strains were taken into account as mecA positive and multidrug-resistant, respectively, that Type I integrons were found in 72.6% and Type II integrons 35.2% of *S. aureus* clinical isolates, respectively [24]. This prevalence is a lower percentage VS global incidences, but in other countries, the scope of these changes is wider and wider, in China, there are several reports that Xu et al. in two separate studies showed that in the primary study of 179 methicillin-resistant *Staphylococcus aureus* isolates 42.5% of MRSA with Type I integrons [14], and in the second investigations of 30 isolates of *Staphylococcus aureus,* 53% (16 isolates) had this gene [25]. In Ren et al. report published in 2013 in China, from 180 isolates of *Staphylococcus aureus*, the positive rate of Type I integrons was 39.44% and the positive rate of Integron2 was 5.88% [26]. Our report revealed that there were not any IntI II in clinical samples and it is a very interesting issue that epidemiological features will need to obvious these differences. In India in 2015 by Maratha et al. 143 isolates were mecA positive and in total, 71% of the MRSA isolates were carriers of Type I integrons, since none of the examined isolates were positive for IntI II and IntI III [27]. Therefore, it can be presumed that the prevalence of other Types of integron other than IntI I is not common in *S. aureus*. It is considered, contrary to our expectation in this work, no significant association was observed within the existence of Type I integrons and the antibiotic susceptibility phenotypes in 57 isolates. It seems that most of the studied isolates lack the target gene cassettes on their integron Type I and other mechanisms are involved in the development of resistance. There were differences between the results of this study and those of other studies in our country and elsewhere in the world. The reason for the difference in the frequency and prevalence of antibiotic resistance was related to the different populations and even hospitals and even between populations of a population that could be associated with irrational antibiotic use in these areas.

A statistically significant association was also observed in integrons positive aminoglycosides consistent with findings from other studies. In 2018, in a study in China, the aminoglycoside resistance of all *S. aureus* isolates that were integron-positive categorized in Type I, while no Types II and III integrons were observed [28].

Also, a relationship was found between the incidence of Type I integron and antibiotic resistance of gentamicin, tetracycline, erythromycin, and co-trimoxazole by Xu et al. This issue representing the existence of various gene cassettes on mobile genetic elements like as integrons and therefore the integrons' role in the incidence of antibiotic resistance in these bacterial isolates [14]. The existing findings approved these MGEs' role in transferring and spreading different drug resistance patterns [19, 21, 28–32]. The high incidence of antibiotic resistance among bacterial pathogens is currently a key public health issue. Within our work, all *S. aureus* isolates had resistance to penicillin (97.9%), consistent with the findings of other studies. However, no high resistance rate was found to gentamicin (47%), clindamycin (37.4%), and amikacin (46.1%). Safari et al. highlighted the great resistance levels in *S. aureus* isolates to clindamycin, gentamicin, and ciprofloxacin, not consistent with our results [33]. The resistance rates to tetracycline (58.3%), gentamicin (47%), ciprofloxacin (50%), and tobramycin (47%) in *S. aureus* isolates were consistent with another report [21, 24, 32–34]. The greatest isolates susceptibility denoted for penicillin (97.9%) and tetracycline (58.3%). In this work, 2.6% of the isolates had resistance to linezolid. In the study of Goudarzi et al., no resistance of the *S. aureus* was found to linezolid [29]; however, Mostafa et al. reported 17.3% of the isolates resistant to this antibiotic [24]. In the study of Poorabbas et al., it was found that the lowest resistance rates were related to co-trimoxazole and rifampin (10%) and clindamycin (24%) [35], however, in the current work, the lowest resistance was to linezolid (2.6%), chloramphenicol (3.4%), and teicoplanin (4.3%).

One of the restrictions of the current work was not an assessment of the frequency of possible gene clusters on integrons. Considering the integrons frequency amongst resistant strains of *S. aureus* and the risk of fast transferring of these agents in these isolates, it is necessary to identify isolates with integrons and their association with patterns of antibiotic resistance, to monitor patterns of resistance, and to choose acceptable antibiotics using genotypic and phenotypic resistance measurement results performed by hospital laboratories that are involved in the reduction of antibiotic resistance.

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Compliance with Ethical Standards

Conflict of interest It is declared by the authors that there are no conflict of interest.

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